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(54) STABILIZATION OF GROWTH PROMOTING HORMONES

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(74) SA

(57) Claim

1. A method for maintaining the fluidity of a growth promoting hormone and maintaining its biological activity upon administration to an animal which method comprises:

(a) forming a mixture of water, a growth promoting hormone and a block copolymer containing polyoxyethylene-polyoxypropylene block copolymer having an average molecular weight of from about 1,100 to about 40,000 wherein the block copolymer is an amount sufficient to prevent the precipitation of the growth hormone upon administration to the animal; and

(b) administering the admixture to the animal.

12. A method for effecting growth promotion in animals which comprises administering to the animal a mixture containing an effective amount of a growth promoting hormone, water and from about .05 to about 50 percent by weight of a block copolymer containing polyoxyethylene-polyoxypropylene units having an average molecular weight of from about 1,100 to about 40,000.

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20. A growth promoting formulation for administration to an animal comprising a mixture of water, an effective amount of a growth promoting hormone and a block copolymer containing polyoxyethylene-polyoxypropylene units and having an average molecular weight of from about 1,100 to about 40,000.

COMMONWEALTH OF AUSTRALIA

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Complete Specification for the invention entitled:

STABILIZATION OF GROWTH PROMOTING HORMONES

The following statement is a full description of this invention, including the best method of performing it known to me:—

This invention relates to a method for maintaining the fluidity of a growth promoting hormone and maintaining its biological activity upon administration to an animal. One major problem in the long term administration of growth promoting hormones is the loss of bioactivity due to the formation of insolubles in aqueous environments. The formation of these insolubles blocks tubing, membranes and various pumps of the implanted delivery devices. System failure almost always eventually results due to the formation of these insolubles.

Another problem associated with the administration of growth hormones is the frequency required and the resulting rise in labor costs necessitated thereby. Moreover, many animals utilized for human food consumption, particularly ruminants, such as cattle and sheep, are range-fed for extended periods of time prior to feedlot development, thus rendering administration by injection of the hormone virtually impossible and economically impractical.

Prior efforts to provide for the long-term release of active agents for medication to animals include incorporating the medication in a polymeric matrix whereby the active ingredient is leached into the surrounding tissues of the animal. One such formulation for sustaining the release of a biological agent is disclosed in U.S. Patent No. 3,737,521. This patent discloses a neck implant for releasing a physiologically active estrus-blocking progestational steroid hormone agent in the neck tissue of a fertile heifer comprising a solid essentially linear polyether urethane polymeric matrix containing the steroid hormone agent.

Another known sustained-release delivery means is disclosed in U.S. Patent No. 4,235,988. This patent describes a delivery means comprising a functionally effective amount of biologically active agent and a hydrophilic linear block polyoxyalkylene-polyurethane copolymer.

U.S. Patent Nos. 4,188,373 and 4,100,271 relate to polymeric pharmaceutical vehicles for delivery of pharmaceutically active chemical materials to mucous membranes. The pharmaceutical carriers are aqueous solutions of certain polyoxyethylene-polyoxypropylene condensates. These polymeric pharmaceutical vehicles are described as providing for increased drug absorbtion by the mucous membrane and prolonged drug action by a factor of two or more. Examples of such drugs which can be incorporated in the polyoxyethylene-polyoxypropylene vehicle include those pharmaceuticals directed to the treatment of ocular conditions. While the pharmaceuticals for the treatment of the eye are extensive, these pharmaceuticals are generally of a low molecular weight and do not suffer from the problems of loss of bioactivity and formation of insolubles upon administration to an animal. Other patents of interest include U.S. Patent Nos. 4,474,751, 4,474,752, 4,474,753 and 4,478,822. These patents are directed to various drug delivery systems comprising polymers which are tetra-substituted derivatives of ethylene diamine, propylene diamine, butylenediamine, pentylenediamine and hexylene diamine. The substituents are block copolymers of polyoxypropylene and polyoxyethylene. Examples of drugs which can be administered in this polymer delivery system include antibacterial substances, anti-inflammatories, anti-parasitics, antiviral effective compounds and peptide drugs such as insulin and somatostatin. The majority of the above drugs have low

molecular weights and therefore are not subject to the formation of insolubles. These patents do not disclose a method for stabilization of growth promoting hormones. Therefore, there exists a need for a method of maintaining the fluidity of a growth promoting hormone and maintaining its biological activity for prolonged release upon administration.

SUMMARY OF THE INVENTION

The present invention provides for a method for maintaining the fluidity of a growth promoting hormone and maintaining its biological activity upon administration to an animal which method comprises:

(a) forming a mixture comprising water, a growth promoting hormone and a block copolymer containing polyoxyethylene-polyoxypropylene units and having an average molecular weight from about 1,100 to about 40,000 wherein the block copolymer is in an amount sufficient to prevent the precipitation of the growth promoting hormone upon administration to the animal; and

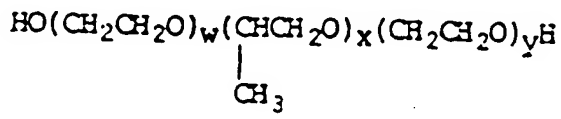
(b) administering the admixture to the animal.

Also disclosed is a method for accelerating growth in animals which comprises administering to the animals a growth promoting formulation comprising an aqueous mixture containing an effective amount of a growth promoting hormone and a block copolymer containing polyoxyethylene-polyoxypropylene units. Surprisingly, these aqueous mixtures preserve the bioactivity and stability of the growth hormone and provide for a prolonged release rate upon administration to the animal.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

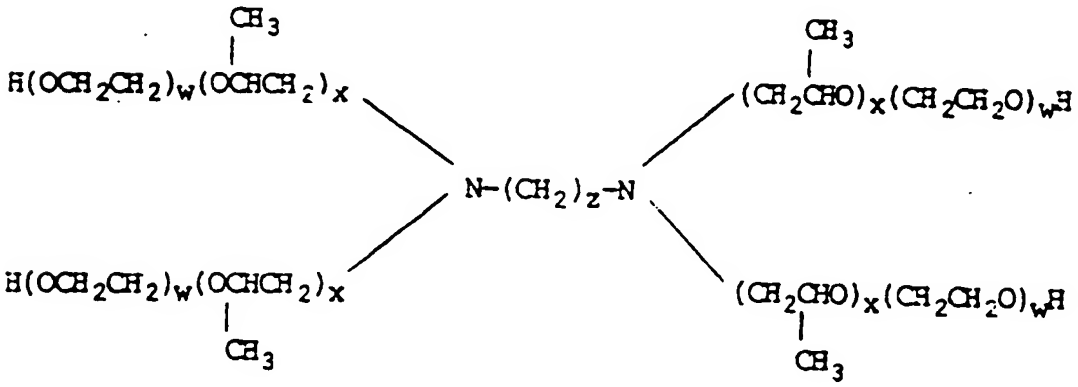
The present invention provides a method of stabilizing growth promoting hormones which are administered to animals. Surprisingly, aqueous solutions of certain polyoxyethylene-polyoxypropylene block copolymers are useful as stabilizers for growth promoting hormone. Another advantage is the achievement of prolonged release rates of the growth hormone upon administration to the animal. The block copolymers for use in accordance with the present invention can be described by the following structural formulas:

Formula 1



and

Formula 2



where z is an integer of from 2 to 6 and wherein the block copolymers of Formula 1 have an average molecular weight of from about 1,100 to about 15,500 and the block copolymers of Formula 2 have an average molecular weight of from about 1,600 to about 40,000 and w, x, and y are any integers within the above constraints.

The block copolymers of Formula 1 generally have an average molecular weight of from about 1,100 to about 15,500, with an average molecular weight of from 11,000 to about 13,000 being preferred. Generally, the polyoxyethylene units are at least 50% of the total number of units in the block copolymer of Formula 1. A particularly preferred block copolymer is when the polyoxyethylene unit is about 70% of the total number of units in the block copolymer. Block copolymers according to Formula 1 are commercially sold by BASF-Wyandotte Corporation of Wyandotte, Michigan under the trademark "PLURONIC". The "PLURONICS" are block copolymers generically classified as polyoxypropylene-polyoxyethylene condensates terminating in primary hydroxyl groups. They are formed by the condensation of propylene oxide into a propylene glycol nucleus followed by the condensation of ethylene oxide onto both ends of the polyoxypropylene base. Examples of PLURONIC" block copolymers include: Pluronic F-68, Pluronic F-77, Pluronic P-75, Pluronic P-65, Pluronic L-64, Pluronic F-87, Pluronic F-88, Pluronic F-98, Pluronic F-108 and Pluronic F-127. One particularly preferred Pluronic is Pluronic F-127. Other commercially available block copolymers classified under Formula 1 are those products sold under the trademark "GENAPOL" by Hoechst AG of Frankfurt, Germany.

The block copolymers of Formula 2 generally have an average molecular weight of from 1,600 to about 40,000, with an average molecular weight of from 15,000 to about 20,000 being preferred. Similar to the block copolymers of Formula 1, the polyoxyethylene units are at least 50% of the total number of units in the block copolymer of Formula 2. Preferably, the polyoxyethylene units are about 70% of the total number of units in the block copolymer. Block copolymers of Formula 2 are also

commercially available from BASF-Wyandotte Corporation. These block copolymers are sold under the trademark "Tetronic®".

The above polyoxyethylene-polyoxypropylene block copolymers must be present in an amount sufficient to stabilize the growth promoting hormone. Since other ingredients are also present in the formulation, such as water and any other optional compounds, the concentration of the block copolymer should also be high enough to result in a suitable gel matrix upon administration to the animal. The block copolymer is generally present in the growth hormone formulation in amounts from about 0.05 to about 50 percent by weight of the total aqueous growth promoting formulation, and preferably from about 1 to about 30 percent by weight of the total aqueous composition.

Aside from serving as a stabilizer for the growth hormone, these block copolymers provide excellent vehicles for the delivery of the growth hormone. One advantage of these block copolymers is that they are physiologically acceptable. Another advantage is their sol-gel transition temperatures. At temperatures at or below room temperature (30°C), aqueous solutions of block copolymers are in a liquid state. Above the temperatures, the aqueous solutions of block copolymers form a gel. Therefore, at lower temperatures a growth promoting formulation can be produced which is suitable for administration to the animal. However, after administration, the block copolymers form an excellent gel matrix for the prolonged release of the polypeptide.

Suitable growth promoting hormones include human, bovine, avian, ovine, equine and porcine growth promoting hormones. Preferably, the hormone is a porcine growth promoting hormone. The growth promoting hormone should be present in the aqueous mixture in an amount effective

to promote growth upon administration to the animal. While the amount of the growth promoting hormone may vary depending on the particular hormone, the type of animal and the desired results, the growth promoting hormone is generally present in amounts of from about .05 to about 10 percent by weight of the total aqueous mixture. Preferably, the growth promoting hormone is present in amounts of from about .10 to about 5 percent of the overall total weight of the aqueous mixture.

The growth hormones for use in the present invention can be derived by extraction and subsequent concentration techniques from the pituitary glands of various animals. Growth hormones which are produced by recombinant DNA methods are also suitable. The amino acid sequences of various hormones which are suitable in the present invention are known. For example, the amino acid sequence of human growth promoting hormones is described in an article by C.H. Li in Kirk-Othmer "Encyclopedia of Chemical Technology", 3rd E., Vol. 12, pp. 549-552. The amino acid sequence of bovine growth hormone is described in an article by R.P. Woychik, Nucleic Acid Res., 10, 7197 (1982). The amino acid sequence of ovine growth hormone is described in an article by C.H. Liu et al., Arch. Biochem. Biophys., 156, 493-508 (1973). The amino acid sequence of porcine growth hormone is described in an article by P.H. Seeburg et al., DNA, 2, 37, 45 (1983). All of the above references describing the amino acid sequences are hereby incorporated by reference in their entirety. In addition to the above, one can also use growth hormones that have been modified by excision of up to 12 amino acid residues from the amino ends of the amino acid sequences.

The block copolymer and the growth promoting hormone are dispersed in an aqueous solution. The

concentration of the water can vary widely depending on a number of factors such as the desired viscosity of the formulation prior to and after administration, the concentration of the growth hormone, temperature of preparation, etc. Generally, the water will be present in amounts of from about 50 to about 99.9 percent by weight of the total weight of the aqueous growth hormone formulation with from about 75 to about 95 percent by weight being preferred.

The aqueous growth promoting hormone formulation may optionally contain various adjuvants which further contribute to the prolonged release rate. Examples of such adjuvants include beeswax, aluminum monostearate and the like. Preferably, the adjuvant is aluminum monostearate.

While the present method involves an aqueous dispersion, one may optionally add various oils to assist in prolonging the release rate of the growth promoting hormone. Examples of such oils include mineral oils and vegetable oils such as sesame oil, peanut oil, soybean oil and the like.

The preparation of the aqueous formulations which are used in the present invention may be formed by simple mechanical mixing. The polyoxyethylene-polyoxypropylene copolymers are known to dissolve at reduced temperatures. Therefore, the preferred method of solubilization of the polymer includes dispersing the block copolymer in an aqeuous solution at temperatures below the sol-gel temperature of the solution of the copolymer. The aqueous mixture can then be stirred, sonicated or shaken to bring about a more rapid solubilization of the polymer in solution. After the aqueous solution of the polymer has been formed, the growth promoting hormone is added. While the above procedure is described as being preferred, the order of addition can be altered and

should be in no way deemed as limiting to the scope of the present invention. After the growth promoting hormone and the block copolymer have been dispersed in an aqueous solution, optional additives, such as buffers, salts, adjuvants, etc., may be added and dissolved.

Since the aqueous growth promoting hormone formulation is intended to be administered to an animal, the pH must be such that it is physiologically acceptable to the animal and does not contribute to the destabilization of the growth promoting hormone. Generally, the pH of an aqueous growth promoting formulation can range from about 5 to about 11 with the preferred pH range being from about 7 to about 10. The pH of the aqueous formulation can be adjusted by adding effective amounts of a pharmaceutically acceptable buffer to obtain the required pH. Suitable pharmaceutically acceptable buffers are generally known to those skilled in the art.

This invention additionally provides a method for effecting growth promotion in animals which comprises administering to the animal an effective amount of a prolonged release formulation comprising from about 0.05 to about 50 percent by weight of a polyoxyethylene-polyoxypropylene block copolymer having an average molecular weight of from about 1,100 to about 50,000 with from about .05 to about 10 percent by weight of a growth promoting growth hormone and from about 50 to about 99.9 percent of water. A preferred method according to the present invention comprises administering an effective amount of a prolonged release formulation comprising from about 1 to about 30 percent by weight of a polyoxyethylene-polyoxypropylene block copolymer having an average molecular weight of about from 11,000 to about 13,000 and about .5 to about 5 percent by weight of a porcine growth promoting hormone and from about 75 to

about 95 percent by weight of a phosphate buffered saline solution.

The present invention also provides for a growth promoting formulation having improved stability against the formation of insolubles comprising from about .05 to about 50 percent by weight of a block copolymer containing polyoxyethylene-polypropylene units and having an average molecular weight of from about 1,100 to about 40,000 with about .05 to about 10 percent by weight of a growth promoting hormone and from about 50 to about 99.9 percent by weight of water.

The growth promoting hormone formulations are for administration to an animal and preferably a ruminant. These formulation can be administered in a variety of ways. In one embodiment of the present invention, the aqueous solution is administered by subcutaneous or intramuscular injection. Another embodiment of the present invention is to administer the formulation to a reservoir of an implanted device having a means capable of delivering an effective amount of the aqueous polypeptide formulation. A number of delivery means which are implanted in the animals are known to those skilled in the art and are contemplated for use with the formulations of the present invention.

The present invention is illustrated in further detail by way of the following examples which, however, are not to be construed as limiting the scope thereof.

EXAMPLE 1

Isotonic physiological phosphate buffer (PBS) having a pH of 7.3 was prepared from sodium hydrogen phosphates (0.1 M phosphates) plus 0.2 percent NaN_3. Using this buffer, a solution of 18 percent by weight of PLURONIC F 127 was prepared by mechanical mixing. Then a

ca. 40 mg portion of porcine growth hormone (IMC Lot No. CP005-CDE-94.1) in a 50 ml sterile centrifuge tube was wetted with 100 µl of the solution. As a control, another ca. 40 mg portion of the same growth hormone was wetted with 100 µl of PBS solution containing no additives. The tubes were stored at 37°C. Following the 14 days at 37°C, each 50 ml tube was typically handled as follows. First, 40 ml of PBS was added to the tube (defined as start of solubilization time). Using a cup sonicator, the wetted material in the tube was effectively suspended/dissolved. The resulting suspension was subsequently vortexed during a period of standing at room temperature. The respective tube was centrifuged for ca. 5 min. X 1900 G (defined as the end of solubilization time). The resulting supernatant was nearly all removed by pipet and the undissolved residue suspended in 20 ml added water. Following centrifugation and supernatant removal, the residue in the tube was dried at room temperature in a Savant Speed Vac Concentrator to a final chamber pressure of ca. 150 millitorr. The pelleted dry residue was removed from the tube and its weight determined by the different weight of the tube.

It is apparent from the Table below that a significant decrease in the rate of formation of insolubles is achieved by use of the stabilizer of the present invention.

TABLE 1

	PBS Solution	18% by weight PLURONIC F127/ PBS Solution
rpGH	IMC Lot No. CF005-CDE94.1	IMC Lot No. CF005-CDE94.1
Days @ 37°C	14	14
Solubilization Time (hrs)	1.5	1.5
Insolubles as Wt % of Starting rpGH	67	43

EXAMPLE 2

In an effort to demonstrate the ability of the stabilizers of the present invention to preserve high levels of bioactivity of growth hormones, the following experiments were conducted.

A first solution (Solution A) was prepared which consisted of a phosphate buffered saline solution (PBS) containing recombinant porcine growth hormone (IMC Lot No. 01-00A.94.1) in a concentration of 1 mg/ml of PBS. A second solution (Solution B) was prepared which was identical to the first solution but additionally contained 5 weight percent of PLURONIC F 127. Each solution was then placed in a peristaltic pump and continuously circulated at room temperature for a period of 24 hours. The two solutions were then removed from the circulation device.

Each solution was then diluted in order to administer varying concentrations of the growth hormone solutions to rats (See Table 2 below for concentrations). As another control, an uncirculated solution (Solution C) identical to solution A was prepared and then diluted.

Each diluted solution was administered to a number of rats. Only one injection was given. The weight gain of each rat was then determined after 10 days following the administration of the solution. Table 2 below lists the dosage of the growth hormone that was administered, the percentage of weight gain and the relative potency of the growth hormone.

The data in the table below demonstrates that the relative potency of a circulated growth hormone which contains a stabilizer (Solution B) is higher than circulated unstabilized solutions (Solution A) and is equal to uncirculated growth hormone solutions (Solution C).

TABLE 2

SOLUTION	DOSE (µg)	NO. OF RATS	% WEIGHT GAIN MEAN	% WEIGHT GAIN STD. DEV. (+/-)	% RELATIVE POTENCY*
Solution A (rpGH+PBS)	6	10	7.1	3.2	21
	12	10	10.2	3.4	
	24	10	12.0	3.3	
Solution B (rpGH+5% PLUORINIC/PBS)	6	5	9.2	2.1	33
	12	9	9.9	5.3	
	24	10	15.5	1.9	
Solution C (rpGH+PBS)	6	9	10.2	3.3	33
	12	10	11.4	4.1	
	24	10	13.4	3.6	

* Value derived from all dosage ranges of Solutions, i.e., A, B, and C.

The claims form part of the disclosure of this specification.

CLAIMS

The claims defining the invention are as follows:

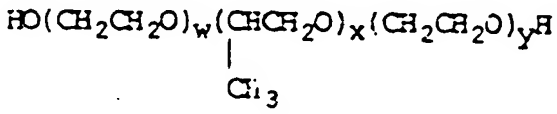
1. A method for maintaining the fluidity of a growth promoting hormone and maintaining its biological activity upon administration to an animal which method comprises:

(a) forming a mixture of water, a growth promoting hormone and a block copolymer containing polyoxyethylene-polyoxypropylene block copolymer having an average molecular weight of from about 1,100 to about 40,000 wherein the block copolymer is an amount sufficient to prevent the precipitation of the growth hormone upon administration to the animal; and

(b) administering the admixture to the animal.

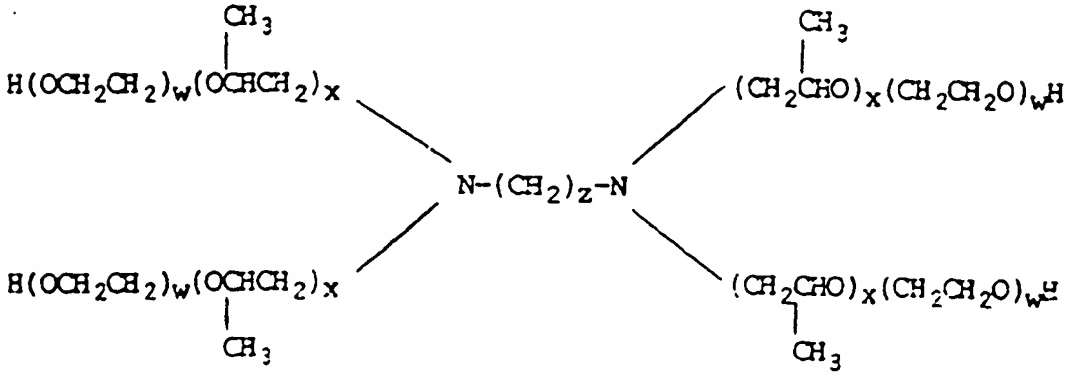
2. The method of claim 1, wherein said polymer containing polyoxyethylene-polyoxypropylene units is selected from the following structural formula:

Formula 1



and

Formula 2



where z is an integer of from 2 to 6 and wherein the block copolymers of Formula 1 have an average molecular weight of from about 1,100 to about 15,500 and the block copolymers of Formula 2 have an average molecular weight of from about 1,600 to about 40,000 and w, x, and y are any integers within the above constraints.

3. The method of claim 1, wherein the polyoxyethylene-polyoxypropylene block copolymer is present in amounts of from about .05 to about 50 percent of the total weight of the mixture.

4. The method of claim 1, wherein the number of polyoxyethylene units is at least 50 percent of the total units in said block copolymer.

5. The method of claim 4, wherein the number of polyoxyethylene units is about 70 percent of the total units in said block copolymer.

6. The method of claim 1, wherein the average molecular weight of said block copolymer is from about 11,000 to about 12,000.

7. The method of claim 1, wherein the mixture of block copolymer, water and a physiologically active polypeptide composition additionally contains a buffer.

8. The method of claim 1, wherein the mixture is administered to a reservoir of a drug delivery device which is implanted in an animal.

9. The method of claim 1, wherein the mixture is administered by subcutaneous or intramuscular injection.

10. The method of claim 1, wherein said growth promoting hormone is human, bovine, avian, porcine, equine and ovine growth promoting hormones.

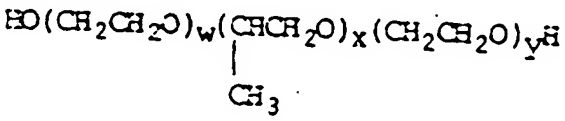
11. The method of claim 10, wherein said growth promoting hormone is porcine growth promoting hormone.

12. A method for effecting growth promotion in animals which comprises administering to the animal a mixture containing an effective amount of a growth

promoting hormone, water and from about .05 to about 50 percent by weight of a block copolymer containing polyoxyethylene-polyoxypropylene units having an average molecular weight of from about 1,100 to about 40,000.

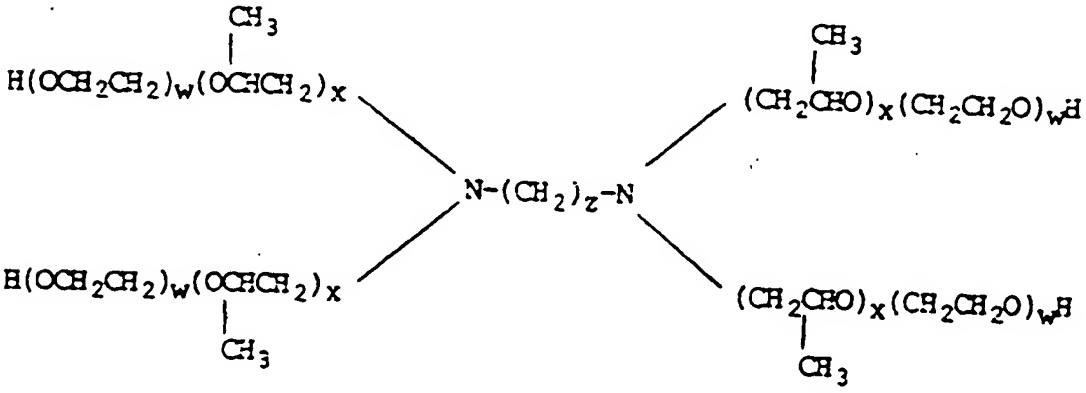
13. The method of claim 12, wherein said polymer containing polyoxyethylene-polyoxypropylene units is selected from the following structural formula:

Formula 1



and

Formula 2



where z is an integer of from 2 to 6 and wherein the block copolymers of Formula 1 have an average molecular weight of from about 1,100 to about 15,500 and the block copolymers of Formula 2 have an average molecular weight of from about 1,600 to about 40,000 and w, x, and y are any integers within the above constraints.

14. The method of claim 12, wherein said growth hormone is present in amounts of from about .05 to about 10 percent by weight of the total mixture.

15. The method of claim 12, wherein said water is present in amounts of from 50 to about 99.9 percent of the total weight of the mixture.

16. The method of claim 12, wherein said growth promoting hormone is selected from human, porcine, aquine, bovine, avian and ovine growth promoting hormones.

17. The method of claim 16, wherein said growth promoting hormone is porcine.

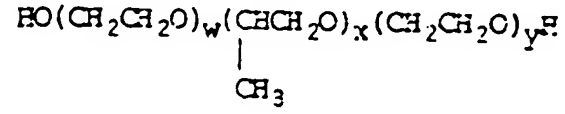
18. The method of claim 12, wherein said mixture is administered by subcutaneous or intramuscular injection.

19. The method of claim 12, wherein said mixture is administered by an implanted delivery device means.

20. A growth promoting formulation for administration to an animal comprising a mixture of water, an effective amount of a growth promoting hormone and a block copolymer containing polyoxyethylene-polyoxypropylene units and having an average molecular weight of from about 1,100 to about 40,000.

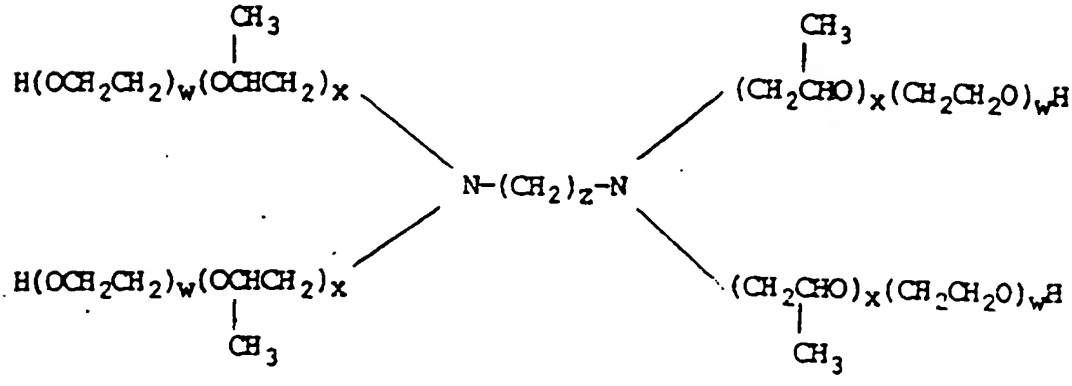
21. The growth promoting formulation of claim 20, wherein said block copolymer is selected from the following structural formulas:

Formula 1



and

Formula 2



where z is an integer of from 2 to 6 and wherein the block copolymers of Formula 1 have an average molecular weight of from about 1,100 to about 15,500 and the block copolymers of Formula 2 have an average molecular weight of from about 1,600 to about 40,000 and w, x, and y are any integers within the above constraints.

22. The growth promoting formulation of claim 20, wherein said polyoxyethylene-polyoxypropylene block copolymer is present in amount of from .05 to about 50 percent by weight, said growth promoting hormone is present in amounts of from .05 to about 10 percent by weight and said water is present in amounts of from about 50 to about 99.9 percent by weight wherein all percentages by weight are based on the total weight of the growth promoting formulation.

23. The growth promoting formulation of claim 20, wherein said mixture additionally contains an oil.

24. The growth promoting formulation of claim 23, wherein said oil is selected from the group consisting of mineral oil, sesame seed oil, soybean oil and peanut oil.

25. The growth promoting formulation of claim 20, wherein said mixture additionally contains an adjuvant.

26. The growth promoting formulation of claim 25, wherein said adjuvant is selected from the group consisting of beeswax and aluminum monostearate.

27. The growth promoting formulation of claim 20, wherein said mixture has a pH of from 5 to 11.

28. The growth promoting formulation of claim 20, wherein said mixture additionally contains a buffer.

29. A method of maintaining the fluidity of a growth promoting hormone or a method of promoting growth or a growth promoting formulation substantially as hereinbefore described with reference to any one of the accompanying Examples.

30. The articles, things, parts, elements, steps, features, methods, processes, compounds and compositions referred to or indicated in the specification and/or claims of the application individually or collectively, and any and all combinations of any two or more of such.

DATED THIS 29th July 1988
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